Remarks and Arguments

Upon entry of the foregoing amendment, claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 29-42, 44-56, 60, and 61 are pending in the application, with claim 1 being the independent claim. Claims 29-31, and 35-37 have previously been withdrawn from prosecution. As process claims which depend from and include all the limitations of the product claims currently under examination, Applicants reserve the right to request rejoinder and examination of the withdrawn claims should the product claims be found allowable. Claims 28, 43, and 57-59 have been previously sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the subject matter of all earlier pending claims in related applications. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Claim 1 have been amended. Support for the amendment to claim 1 adding the limitation "rigid" can be found in International Patent Application No. PCT/DK02/00229, which corresponds to the U.S. Patent No. 7,713,942 (hereinafter "Dalsgaard") on page 22, lines 21-24, which is incorporated into the instant application by reference in paragraph [0126]. Accordingly, no new matter has been added by these amendments.

The specification has been amended to include priority claims to a Danish priority application and a U.S. Provisional Application. These priority claims are noted in PCT/DK03/000654, therefore no new matter is introduced by this amendment. The specification has also been amended to include a statement indicating names of parties to a Joint Research Agreement. No new matter has been added by this amendment.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60, and 61 under 35 U.S.C. § 102(b) as allegedly being anticipated by Foldvari *et al.* (WO 99/11247, hereinafter "Foldvari") (Office Action, hereinafter "OA," at page 3). Applicants respectfully traverse this rejection.

Specifically, the rejected claims all recite a construct for transdermal delivery of an immunogen comprising at least one ***cationic sterol***. The Examiner argues that Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol, and cholestane. Furthermore, the Examiner maintains her assertion that "absent evidence to the contrary, the sterol of Foldvari encompasses a cationic sterol." (OA at pager 4). Applicants respectfully disagree. The term "cationic sterol" is defined in Dalsgaard on page 27, lines 8-9 as "a sterol carrying a net ***positive*** charge at pH 7.0" (emphasis added). Cholesterol, coprostanol, cholestanol, and cholestane are steroid precursors or metabolites, all of which carry a net ***neutral*** charge at pH 7.0. To illustrate this point, Applicants have previously submitted a copy of pages from the Merck index (Exhibit A of the Supplemental Amendment and Reply dated January 5, 2010) describing compounds (5α)-Cholestane (2199), Cholestanol (2200), Cholesterol (2201), and Coprosterol (also known as choprostanol) (2524). Applicants respectfully draw the Examiner's attention to the fact that none of these compounds have groups that are ionizable at pH 7.0. The claim is anticipated by a reference only if the reference teaches

each and every element of the claim. (MPEP § 2131.) Foldvari does not disclose a construct for transdermal delivery comprising ***cationic*** sterols, and thus does not anticipate any of the claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 57, 60, and 61 .

Furthermore, in an effort to advance prosecution, and not in acquiescence to any pending rejections, Applicants have amended claim 1 to recite that the complex adopts a micro-particle structure in the form of a ***rigid*** cage-like matrix. Support for this amendment is found in Dalsgaard, which specifies that the term "Iscom structure" as "***[r]igid*** cage-like matrix characterized by an icosahedral symmetry" (*See* page 22, lines 21-24, emphasis added).

In contrast, Foldvari discloses a composition of flexible lipid vesicles (liposomes) for transdermal administration of immunogen, wherein a lipid vesicle is composed of a series of ***lipid bilayers***. Foldvari at p. 6, ll. 1-7 and Figure 1, emphasis added. Applicants have previously provided a figure from Chapter 9 entitled "Liposomes and ISCOMs" of "Novel Vaccine Strategies," S.H.E. Kaufmann (*ed.*) Wiley (2004), p. 174, comparing a diagrammatic representations and electron micrographs of liposomes (panel A) and ISCOMs (panel D). (Exhibit B of the Supplemental Amendment and Reply dated January 5, 2010.) As can be seen from panel A, liposomes do not adopt the distinctive micro-particle structure in the form of a rigid cage-like matrix typical of ISCOMs (panel D), and as required by the currently pending claims.

Lastly, the Examiner stated that since the Office does not have facilities for examining currently claimed composition with the composition of the prior art, the burden is placed on Applicants to demonstrate differences between the claimed

composition and the prior art. (OA at page 6). Applicants believe that examination of the provided electron micrographs (Exhibit B of the Supplemental Amendment and Reply dated January 5, 2010) of liposomes (structures disclosed in Foldvari) and rigid cage-like matrix of ISCOM (structures claimed herein) offers such demonstration. As such, Applicants respectfully assert that their burden in providing novel and unobvious differences between claimed invention and the prior art is met, and it is respectfully requested that the Examiner withdraw the rejection.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32-34, 38-42, 46-56, 60, and 61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari and British Pharmacopoeia 1993 (herein after "BP"). (OA at page 7). Applicants respectfully traverse this rejection.

As alleged in the Supplemental Amendment and Reply dated January 5, 2010, the Examiner has not met the burden of establishing a *prima facie* case of obviousness based on the Examination Guidelines. Specifically, the Examiner has not established that the ordinary artisan reading Foldvari and BP in combination would arrive at the presently claimed construct for transdermal delivery of a complex comprising a saponin and a ***cationic sterol*** which adopts a micro-particle structure in the form of a ***rigid cage-like matrix***. Foldvari is directed to ***flexible*** lipid bilayer structures which ***fully enclose*** an oil in water emulsion. Nothing in Foldvari would even vaguely lead the skilled person to consider the use of rigid microparticles in the form of a rigid cage-like matrix. Indeed, even the unskilled person would understand that an oil in water emulsion could simply not be contained by a microparticle with a cage-like matrix. Furthermore, the Examiner

stated that Foldvari discloses "an immunogen delivery system comprising at least one ***cationic*** sterol and at least one saponin." (OA at p. 8, emphasis added). However, Applicants respectfully assert that the delivery system of Forldvari does not contain a cationic sterol. The only sterols that are recited in Forldvari are cholesterol, coprostanol, cholestanol, and cholestane. (Foldvari at p. 8, ll. 21-22). The Examiner alleges that "absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol." (OA at p. 8). However, as discussed above, sterols disclosed in Foldvari are not cationic sterols, because none of them carry a net positive charge at pH 7.0. The Examiner further alleges that "there is nothing in the specification that requires cationic sterols to carry a net positive charge at pH 7.0." *Id.* Applicants respectfully contend the erroneous nature of this assertion, as the definition of cationic sterol offered in Dalsgaard on page 27, lines 8-9 specifies that cationic sterol is "a sterol carrying a net positive charge at pH 7.0."

With regards to the BP reference, the Examiner stated that it teaches wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing. (OA at p. 10). Furthermore, the Examiner argued that "it would have been obvious at the time the invention was made to use the hydrocolloid dressing of British Pharmacopoeia 1993 because . . . the combination would have yielded predictable results." (OA at p. 11). Nothing in the BP reference cures the shortcomings of Foldvari as discussed above, nor would the BP reference predictably lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system comprising complex, which assumes a microparticle structure in the form of a rigid cage-like matrix, and which comprises a cationic sterol. Therefore, the art cited by

the Examiner would not have provided a reasonable expectation of success in obtaining the presently claimed cage-like complexes comprising cationic sterols because the mere substitution or combination of elements from the two references cited by the Examiner would not have predictably resulted in a construct for transdermal delivery of immunogenic agents comprising a complex formed of a saponin and a cationic sterol, which adopts a micro-particle structure in the form of a cage-like matrix. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

The Examiner further rejected claims 1, 2, 4, 5, 7-9, 10, 13, 16-23, 25-27, 32-34, 38-43, 46, 47, 49-55, 60, and 61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari and Lee *et al.*, *Intl. J. Pharm.* (2001) 221:1-22 (hereinafter as "Lee"). Applicants respectfully traverse this rejection.

Applicants respectfully contend that Examiner has not established that the ordinary artisan reading Foldvari and Lee in combination would arrive at the presently claimed construct. The Examiner stated that Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol, and cholestane, and that "absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol." (OA at p. 13). As discussed above, sterols disclosed in Foldvari are not cationic sterols, because none of them carry a net positive charge at pH 7.0. The Lee reference discloses that hydrogels have been widely used as a drug carries. According to the Examiner,

> It would have been obvious at the time the invention was made to use hydrogel because of its ease in manufacturing and self application (see Lee et al. at Page 10). Moreover, it would have been obvious at the time the invention was made to use the cross-linked hydrogel because all the claimed elements were known in the prior art and one skilled in the art

> could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

(OA at p. 15).

Just as with the BP reference, nothing in the Lee reference cures the shortcomings of Foldvari as discussed above, nor would the Lee reference predictably lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system comprising complex, which assumes a microparticle structure in the form of a rigid cage-like matrix, and which comprises a cationic sterol. Therefore, for the reasons discussed above, the combinations of references cited by the Examiner would not have predictably led the skilled artisan to the presently claimed cage-like complexes comprising cationic sterols just by performing the mere substitution or combination of elements from the two references. Therefore, Applicants respectfully request withdrawal of the rejection as it relates to the currently pending claims.

New Grounds of Rejections - Rejection Under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60, and 61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60, and 61, and further in view of Kirkby *et al.*, US 2004/0185057 A1 (hereinafter as "Kirkby"). In addition, the Examiner rejected claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-56, 60, and 61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari and Kirkby as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60, and 61, and further in view of BP. The Examiner also rejected claims 1, 2, 4, 5, 7-9, 10, 13, 16-18, 20, 21, 23, 25-

27, 32, 34, 38-42, 44-56, 60, and 61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari and Kirkby as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60, and 61, and further in view of Lee. Applicants respectfully traverse these rejections.

Solely to advance prosecution, and not in acquiescence to the propriety of the Examiner's rejections, Applicants provide the following remarks regarding the Kirkby reference. The filing date of Kirby is June 14, 2002. Present application claims priority benefit of U.S. Provisional Application No. 60/415,102, which was filed on October 2, 2002. Therefore, Kirkby reference qualifies as prior art only under 35 U.S.C. § 102(e).

Pursuant to 35 U.S.C. § 103(c),

> (c)(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> (2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if
>
> (A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;
>
> (B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and
>
> (C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

35 U.S.C. § 103(c).

The presently claimed subject matter was developed as a result of a joint research agreement (hereinafter as "JRA") between Coloplast A/S and Pharomed A/S (currently Nordic Vaccine Technology A/S). The JRA between Pharomed A/S and Coloplast A/S was in effect on the date the claimed invention was made, and the claimed invention was made as a result of the JRA. Furthermore, the International Patent Application No. PCT/DK2003/000654, which corresponds to the U.S. Application No. 10/529,873, lists Pharomed A/S and Coloplast A/S as co-applicants. The International Patent Application No. PCT/DK02/00404, which corresponds to Kirkby, lists Pharomed A/S as the applicant. Pharomed A/S changed its name to Nordic Vaccine Technology A/S in 2004. In compliance with regulations, Applicants have amended the specification to refer to the JRA, and submit herewith a statement under 37 C.F.R. § 1.104(c)(4)(iii) with the requisite fee.

Therefore, pursuant to 35 U.S.C. § 103(c), Kirby can not be applied as a reference under 35 U.S.C. § 103(a). In view of these remarks, Applicants respectfully request that the rejections of claims 1, 2, 4, 5, 7-9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-56, 60, and 61 over Foldvari in view of Kirkby and/or Lee or BP be reconsidered and withdrawn.

Conclusion

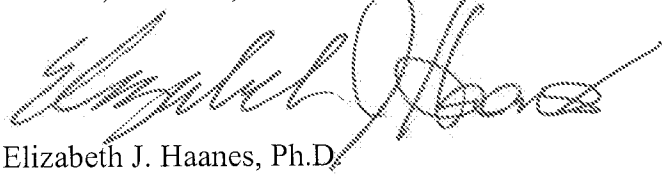
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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